PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*) 18 JUL 2006

Applicant's or agent's file reference
11543-06-228

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/22071	20 June 2005 (20.06.2005)	19 June 2004 (19.06.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): C12Q 1/00(2006.01);G01N 33/48(2006.01) C12Q 1/00(2006.01);G01N 33/48(2006.01)
USPC: 435/4;702/19

Applicant

CHONDROGENE, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	24 May 2006 (24.05.2006)	Jerry Lin
Facsimile No. (571) 273-3201		Telephone No. (571) 272 1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/22071

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-81

Form PCT/ISA/237 (Box No. IV) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/22071

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 6-7, 12, 21, 32, 37-78, 81	YES
	Claims 1-5, 8-11, 13-20, 22-28, 31, 33-36, 79, 80	NO
Inventive step (IS)	Claims 32, 37-78, 81	YES
	Claims 1-31, 33-36, 79, 80	NO
Industrial applicability (IA)	Claims 1-81	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Form PCT/ISA/237 (Box No. V) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-5, 8-11, 13-20, 22-28, 31, 33-36, 79 and 80 lack novelty under PCT Article 33(2) as being anticipated by Pressman et al. (US #2003/80104499 A1).

Regarding claims 1, 2, 13, 14, 20, and 80, Pressman et al. teach a method wherein molecular markers that is reflective of the expression is obtained from two populations (page 9, paragraph 0083; page 35, paragraph 0366) containing a first and second trait subgroup (page 9, paragraph 0083); selecting a plurality of candidate molecular markers (page 9, paragraph 0084-0085); generating a plurality of classifiers by applying a mathematical model to the molecular marker data (page 10, paragraph 0092; page 28, paragraph 0265-0266); and selecting one or more classifiers based on the ability to discriminate between the members of the first and second groups (page 10, paragraph 0092; page 28, paragraph 0265-0266).

Regarding claims 3-5 and 8-11, Pressman et al. teach wherein the ability to discriminate is based on a measure of statistical significance (pages 35-36, paragraph 0376) or differential fold change (page 14, paragraph 0127); wherein the p value is less than 0.01 for less than 50 molecular markers (page 30, paragraph 0313-0315).

Regarding claims 15-18, Pressman et al. teach wherein the plurality of combination include all possible combination of the molecular markers (page 11, paragraph 0098).

Regarding claim 19 and 35, Pressman et al. teach obtaining a third or fourth molecular marker (page 30, paragraph 0302); assigning a score for each classifier (page 30, paragraph 0304); selecting one or more classifier based on the score (page 30, paragraph 0307).

Regarding claims 22-26, Pressman et al. teach using ROC to score classifiers (page 35-36, paragraph 0376) and selecting classifiers with a score greater than 0.90 (page 36, paragraph 0397).

Regarding claim 27, Pressman et al. teach obtaining marker data from a database (page 32, paragraph 0329).

Regarding claim 28, Pressman et al. teach a data collection method that allows for the collection of expression data corresponding to markers for a major portion of the genome (page 28, paragraph 0262).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

Regarding claim 31, Pressman et al. teach where the model is a linear discriminate analysis (page 10, paragraph 0092).

Regarding claims 33 and 34, Pressman et al. teach wherein the number of molecular markers selected is less than 50 molecular markers (page 36, table 25).

Regarding claim 36, Pressman et al. teach receiving data over the internet from a remote source (page 10, paragraph 0094).

Regarding claim 79, Pressman et al. teach a biochemical device for obtaining data from a test subject (page 9, paragraph 0082-0083); a computing device (page 10, paragraph 0094), and a display (page 10, paragraph 0094).

Claims 6, 7, 21, 29, and 30 lack an inventive step under PCT Article 33(3) as being obvious over Pressman et al (US #2003/80104499 A1) in view of Twine et al. (US #2004/0110221 A1).

Pressman et al. is applied as above.
Twine et al. disclose molecular markers wherein the differential fold change is greater than 3.0 (page 72, paragraph 0599; Table 6); ranking the top ten classifiers based on the score (page 84, Table 8); obtaining data using an microarray or RT-PCR (page 64, paragraph 0513-0514).

It would have been obvious to one of ordinary skill in the art to combine the references of Pressman et al. with Twine et al. to obtain more molecular markers to use in Pressman et al.'s method. Pressman et al.'s method is a generic method of creating classifiers using molecular markers. Thus to use his method to the fullest potential, one of ordinary skill in the art would be motivated to obtain as many molecular markers as possible. Particularly molecular markers that show a high differential fold change in different phenotypes would be of high interest since these markers show the clearest indication of a phenotype. Twine et al. disclose several molecular markers that have high differential fold changes in a particular phenotype. Furthermore, Twine et al. is also interested in creating classifiers to diagnostic purposes. Given the similarity of the subject matter between the two references as well as the motivation to find highly differential phenotypes, one of ordinary skill in the art at the time of the invention would be motivated to combine the two references.

Claim 12 lacks an inventive step under PCT Article 33(3) as being obvious over Pressman et al (US #2003/80104499 A1) in view of Tamayo et al. (US #2003/0073083 A1).

Pressman et al. is applied as above.
Tamayo et al. teach applying the Kolmogorov-Smimov test to assess classifiers (page 23,paragraph 0186).

It would have been obvious to one of ordinary skill in the art to combine references of Pressman et al. with Tamayo et al. Pressman et al. disclose several statistical methods of analyzing classifiers. Tamayo et al. also disclose server statistical methods of analyzing classifiers. However Pressman et al. does not teach a method to test the distribution of accuracies of his classifiers. One of ordinary skill in the art would need to know the distribution of accuracies to fully understand the validity of Pressman et al.'s classifiers. Tamayo et al. teach a method of determining the distribution of accuracies of his classifiers using the Kolmogorov-Smimov test. Thus one of ordinary skill in the art would be motivated to incorporate the method of Tamayo et al. with Pressman et al.

Claims 32, 37-78 and 81 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest using bagging boosting, Random Subspace method for optimizing the mathematical model, or selecting markers from Tables 1A-7I using Table F as the criteria.

Claims 1-81 meet the criteria set out in PCT Article 33(4), and thus has industrial applicability because the subject matter claimed can be made or used in industry for the purpose of creating classifiers for identifying traits.